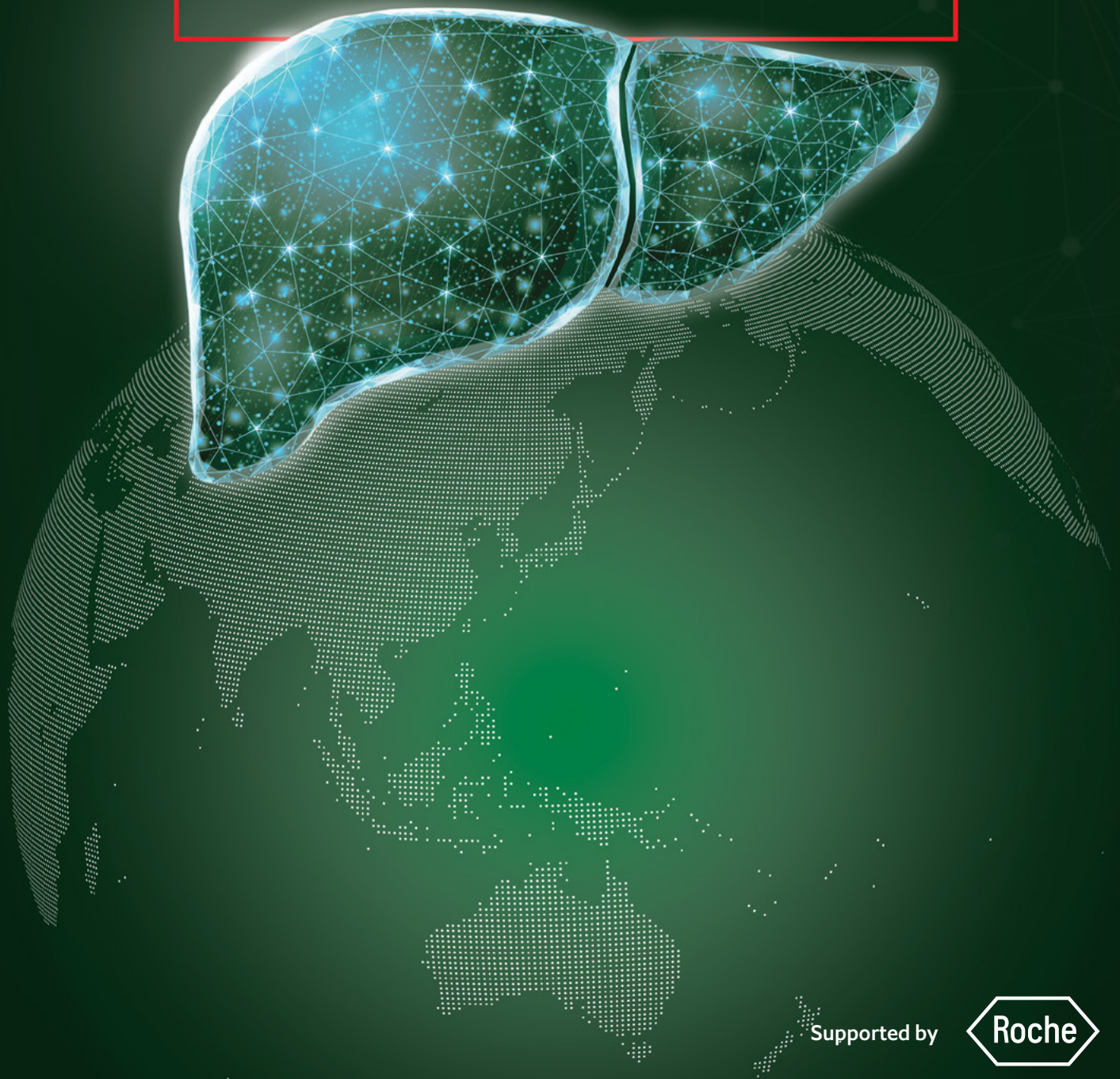
ECONOMIST IMPACT

Building modern hepatocellular carcinoma surveillance programmes:

taking steps to address a leading cause of liver cancer death in Asia



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About the report

Building modern hepatocellular carcinoma surveillance programmes: taking steps to address a leading cause of liver cancer death in Asia is an Economist Impact report, supported by Roche Diagnostics Asia Pacific Pte Ltd.

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- **Masayuki Kurosaki,** Director of the Department of Gastroenterology and Hepatology, Musashino Red Cross Hospital, Tokyo
- **Jasmine Pwu,** Chief Executive Officer of the Data Science Center, Fu-Jen Catholic University, Taiwan
- **Shiv Kumar Sarin,** gastroenterologist and hepatologist; Chancellor, Institute of Liver and Biliary Sciences, New Delhi; Former Chairman of the Board of Governors, Medical Council of India
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Executive summary

Hepatocellular carcinoma (HCC) is a leading cause of cancer mortality in Asia, and its incidence is expected to peak within the next decade. Viral hepatitis B and C infections are the primary drivers of HCC in the region. However, metabolic disorders, such as non-alcoholic liver disease (NAFLD), diabetes and lifestyle-related risk factors are growing as contributors to the HCC burden, reflecting changing lifestyles and demographics.

Given the availability of highly effective interventions for HCC, health systems should prioritise identifying HCC cases early. This will facilitate early intervention, and thereby improve patient outcomes and survival. Systematic surveillance programmes that use appropriate diagnostic tools to identify at-risk patient groups are therefore necessary to mitigate the impact of HCC.

Some of the most comprehensive HCC surveillance programmes are found in Asia. However, their proliferation varies widely across the region. Common barriers to achieving comprehensive surveillance programmes include building political will, the collection and use of epidemiological and real-world data, adequate human and technology resources, sustainable financing, and a lack of public awareness of the benefits of surveillance.

Learning from the well-established programmes, as well as from the challenges identified in economies that have not implemented systematic HCC surveillance thus far, this report highlights several important priorities:

Include HCC surveillance in national programmes and strategic plans.

Where the burden of liver cancer or underlying disease (such as viral hepatitis infection or metabolic disease) is high, HCC surveillance and control must be considered a public health priority. HCC surveillance should be included in national strategic planning where appropriate. Local incidence and prevalence of the disease, as well as existing priorities and resources, should dictate where HCC surveillance fits into the national health strategy. HCC might be included in stand-alone HCC plans, viral hepatitis control plans or broader cancer control plans. When these plans are supported by legislation and funding commitments, country examples show HCC patients experiencing better outcomes. Varying instances of the incorporation of HCC surveillance in strategic plans are seen in Japan, South Korea and Taiwan.

Secure sustainable funding commitments.

In order to be successful, programmes need to consider long-term resourcing and financing for HCC surveillance. Funding decisions should be aligned with evidence-based clinical guidelines and best practices wherever possible. This may require investing in additional ultrasound or advanced imaging equipment, more advanced and optimal testing modalities, trained operators, and laboratory capacity. Decision-makers should be aware that expanding programmes without considering the additional costs of testing and resourcing places extra pressure on health systems.

The appropriate level of funding for HCC surveillance is dictated by established health financing systems and ability to pay. Centralised healthcare coverage may offer the best chance to expand HCC surveillance, but economies could also explore the role of private insurance coverage in increasing access to HCC testing. Where HCC testing is not covered by universal health coverage, out-of-pocket (OOP) expenses can deter attendance and lower take-up rates. When transport costs and the wage loss due to missed employment to attend surveillance are considered, low take-up of HCC testing particularly impacts communities with lower socioeconomic status.

Collect, analyse and utilise data to inform programme design.

Modern approaches must prioritise the collection and analysis of data to inform programme design, devise appropriate surveillance modalities and calculate programme cost-effectiveness**.** Data on HCC epidemiology, patient outcomes, and the human and economic cost of HCC are needed for efficient HCC care. These data should be used by decision-makers to design evidence-based policy, and by relevant stakeholders to advocate for access to surveillance. Effective data sharing is also vital to inform broader public health priorities and update evidence-based clinical practice guidelines. Better data collection and integration will also enable long-term system optimisation and more robust analyses of programmatic impact and outcomes.

Adopt optimal technologies to advance HCC surveillance.

The region must optimise available technologies to improve overall survival of patients through early detection and timely referral for curative treatment. Technology must be adapted to local contextual factors, including epidemiology, resources, and geography. Including tumour markers such as prothrombin induced by vitamin K absence-II (PIVKA-II) and *Lens culinaris* agglutinin-reactive fraction of alpha-fetoprotein (AFP-L3) can help overcome the limitations of ultrasound and AFP testing. The wider use of advanced imaging techniques, or biomarker-based statistical diagnostic models could also benefit HCC patients. This recommendation must be supported by consensus-driven clinical practice guidelines and clear funding commitments. Adapting IT systems to support surveillance programmes can improve access to services and patient recall for both rural and urban areas. With more investment, Artificial Intelligence (AI) systems could further facilitate risk-based surveillance approaches and streamline the interpretation of test results.

Mobilise existing resources for HCC surveillance.

Designing an effective surveillance system does not necessarily require significant new resources. Successful examples of Asian surveillance programmes utilise existing resources and meet the needs of affected populations effectively. Simple solutions seen in the region include expanding the range of healthcare professionals who can diagnose and manage HCC, as well as leveraging existing access points to the health system such as primary are and community health workers. Expanding and formalising the use of private healthcare capacity in HCC care, which has been demonstrably effective in other cancers, should be explored further.

Engage a broad spectrum of stakeholders to further surveillance goals.

A multi-stakeholder engagement approach must be adopted to drive optimal surveillance programmes. Key stakeholders include decision-makers from national and local government, physicians, patients, advocacy groups, payers and industry. The role of national clinical champions to bridge the gap between patients' needs and policymakers' understanding may help to drive progress.

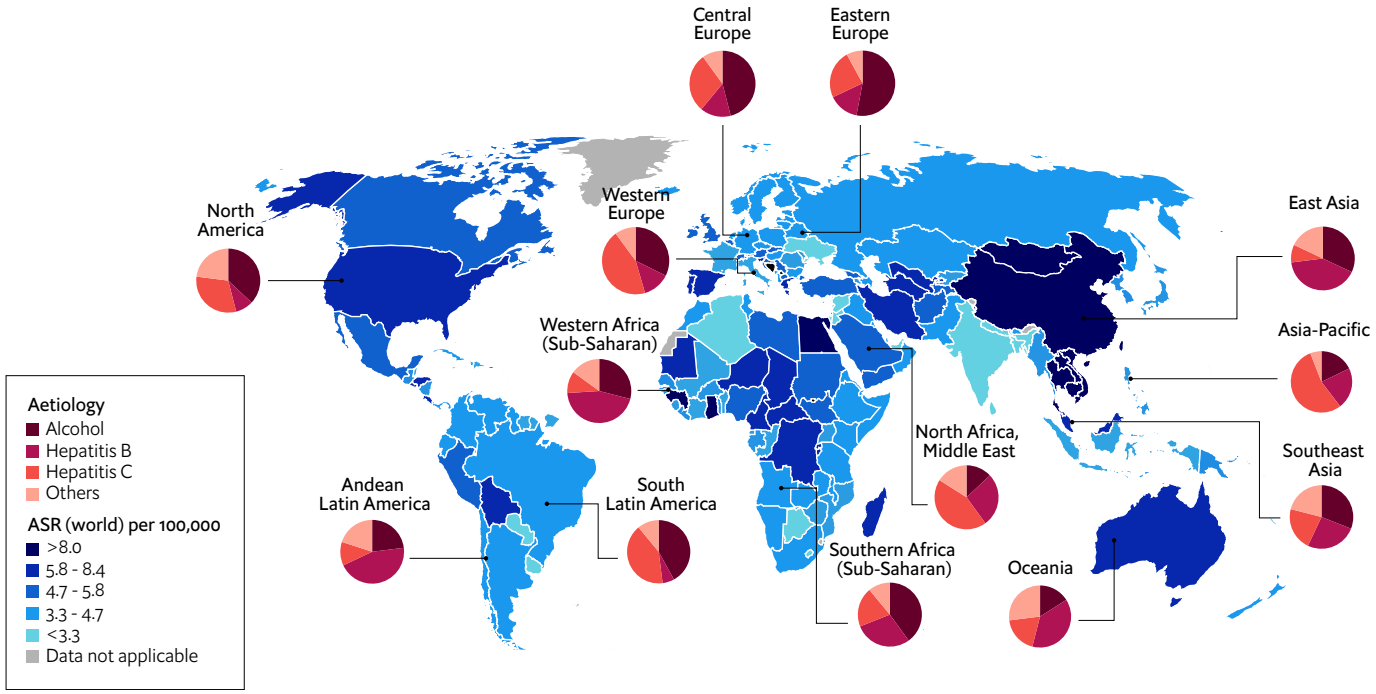
Raise awareness and provide education on the need for HCC surveillance.

The current awareness and knowledge of HCC and surveillance is suboptimal among both healthcare professionals and the general population. This represents a significant and persistent barrier to surveillance uptake and compliance. There are excellent examples of awareness programmes in the region that utilise expertise from both medical experts and non-governmental organisations (NGOs). Learning from these programmes and applying a coordinated approach to HCC surveillance will offer the best chance for success.

Chapter 1. The evolving burden of hepatocellular carcinoma in Asia

Liver cancer will affect an estimated one million people globally by 2025.[1] Over 70% of the global incidence and death from liver cancer currently occurs in Asia, where it is the second-leading cause of cancer deaths after lung cancer.[2] There are several types of liver cancer, but that of the hepatocytes—the primary functional cell of the liver—is the most common. Known as hepatocellular carcinoma (HCC), it accounts for between 75% and 90% of all liver cancers in Asia.[1] Asia has some of the highest age-standardised rates (ASR) of HCC in the world (see **Figure 1**). Chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) is the cause of more than 80% of HCC cases in Asia.[3] Vaccination against HBV has had the single biggest impact on preventing HCC. Cohort data from Taiwan shows significantly lower HCC occurrence in vaccinated cohorts versus unvaccinated ones.[4] Currently, treatment for chronic HBV infection does not offer a cure, but rather aims to suppress the virus and delay progression to liver cirrhosis and HCC. No vaccine exists for HCV. Available therapies offer a "viral cure" for chronic HCV, but this does not completely mitigate the risk of developing HCC.[5] Dietary and lifestyle-related causes of liver disease are increasing at an alarming rate. Metabolic-associated fatty liver disease (MAFLD)—previously also known as non-alcoholic liver disease (NAFLD)—includes patients with liver disease co-morbid with clinical evidence of obesity, type 2 diabetes or other metabolic dysfunction.[6] MAFLD was previously thought to predominantly affect

Figure 1. Age-standardised rate of hepatocellular carcinoma by country and aetiology



ASR, age-standardised rate. Source: adapted from Llovet et al., 2021[1]

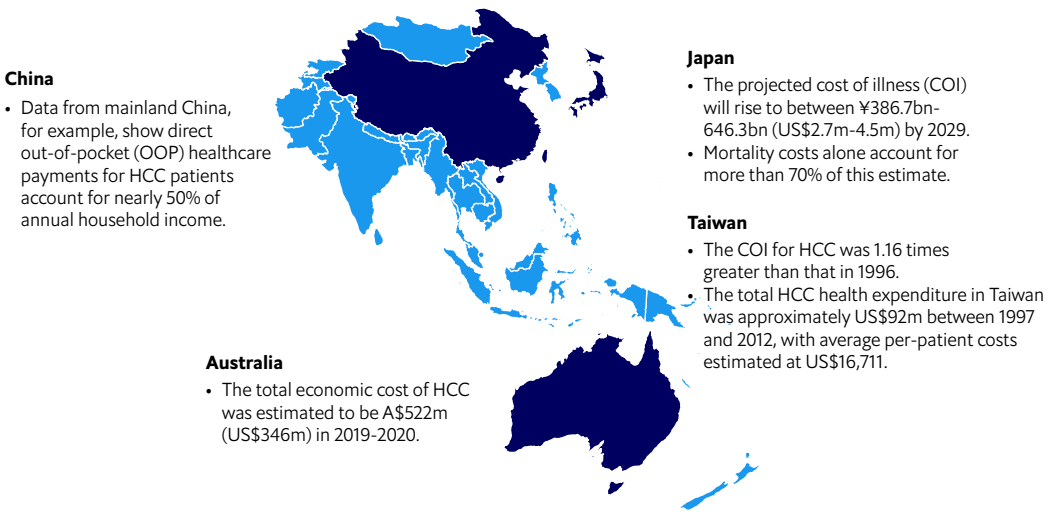
Western populations. However, driven by economic growth and the rising popularity of high caloric diets, nearly 50% of MAFLD-related complications now occur in Asia.[7]

HCCs diagnosed early—referring to those in stages 0–B in the Barcelona Clinic Liver Cancer [BCLC] staging system—are considered treatable via surgery, liver transplant or chemo/radiotherapy.[8] More recently, advances in immuno-oncology therapies have improved chances of survival for patients with advanced, unresectable HCC.[9] Despite advances in the treatment of HCC, the mortality burden in Asia remains substantial. In 2020 there were an estimated 566,269 liver cancer deaths across the region.[10] HCC patients in Asia have a slightly lower survival rate than their European or North American counterparts. A meta-analysis calculated the five-year survival rate to be just 18% across Asian countries.[11] Prognosis varies widely in the region, but is on average higher in more developed economies. The highest survival rates are seen in Japan, where five-year survival reached 58% for those diagnosed in 2010–2013.[12] This is attributable to early identification of cases and the use of highly-effective interventions.

Beyond the human cost of HCC, the economic burden in Asia Pacific is substantial (see **Figure 2**). Globally, liver cancer was estimated to cost INT$1.7trn in 2017, representing 0.036% of total GDP in 2020–2050.[13] In China alone, the overall economic burden of liver cancer was estimated at CNY 76.7bn (US$11.1bn) in 2019, accounting for 0.047% of GDP.[14] In Australia, the total economic cost of HCC was estimated to be A$522m (US$346m) in 2019-2020.[15] Despite steady declines in the incidence of HCC in Japan, the projected cost of illness (COI) will rise to between ¥386.7bn-646.3bn (US$2.7m-4.5m) by 2029.[16] Mortality costs alone account for more than 70% of this estimate. Meanwhile in Taiwan, research shows that the COI for HCC was 1.16 times greater than that in 1996.[17] The total HCC health expenditure in Taiwan was approximately US$92m between 1997 and 2012, with average per-patient costs estimated at US$16,711.[18] What is more concerning is that the costs borne by HCC patients can be catastrophic. Data from mainland China, for example, show direct out-of-pocket (OOP) healthcare payments for HCC patients account for nearly 50% of annual household income.[19]

Given the availability of highly effective interventions for HCC, particularly when they are deployed at the early stages of the disease, health systems need to focus on identifying at-risk patients early to reduce the HCC burden and mortality in the region through comprehensive surveillance programmes. The remainder of this report is dedicated to discussing the options for establishing effective HCC surveillance in Asian economies.

Figure 2. Snapshot of the economic burden of HCC in selected countries in Asia Pacific[15,16,17,18,19]



Chapter 2. The value of hepatocellular carcinoma surveillance

The purpose of HCC surveillance is to identify cases early to enable optimal intervention, thereby improving patient outcomes and survival. The World Health Organization (WHO) defines surveillance as "the continuous and systematic collection, orderly consolidation and evaluation of data with prompt dissemination of results to those who need to know, particularly those who are in a position to take action".[20] For HCC, this requires identifying various different at-risk patient groups by using appropriate diagnostic tools.

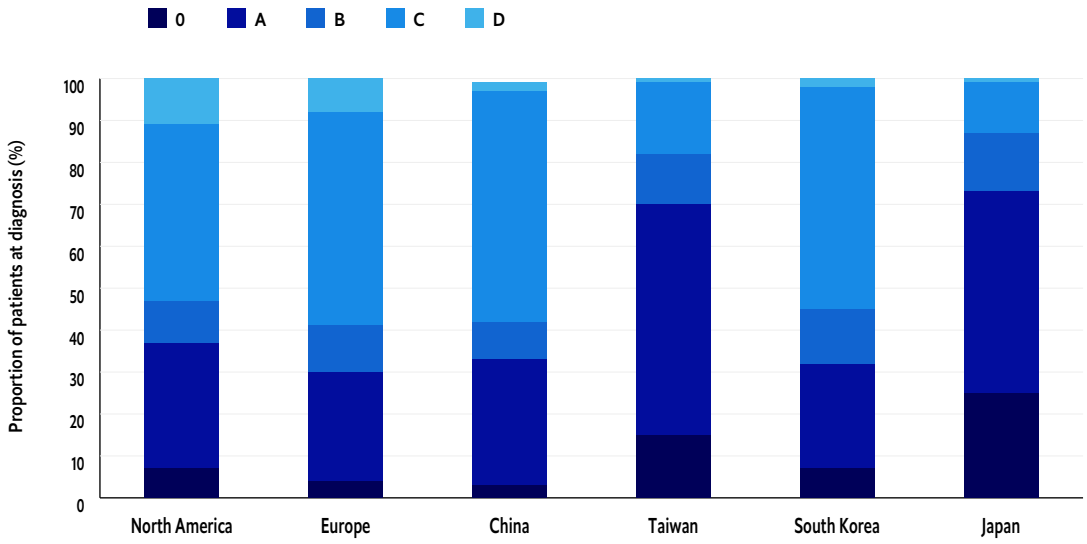
Target groups

HCC is a complex disease with multiple risk factors. As such, target groups for HCC surveillance vary based on the local epidemiology and aetiology (see **Figure 1**).

They include HBV and HCV patients and those with, or at risk of cirrhosis. Those with metabolic syndrome and endocrine diseases who are at increased risk of developing HCC also require surveillance. These conditions include insulin resistance and diabetes, obesity, dyslipidaemia and hypertension.[21] Habitual alcohol and tobacco use are also risk factors for HCC. Alcohol and tobacco act synergistically with other causes of liver diseases.[22] These risks should be particularly monitored in economies with high alcohol and tobacco use.

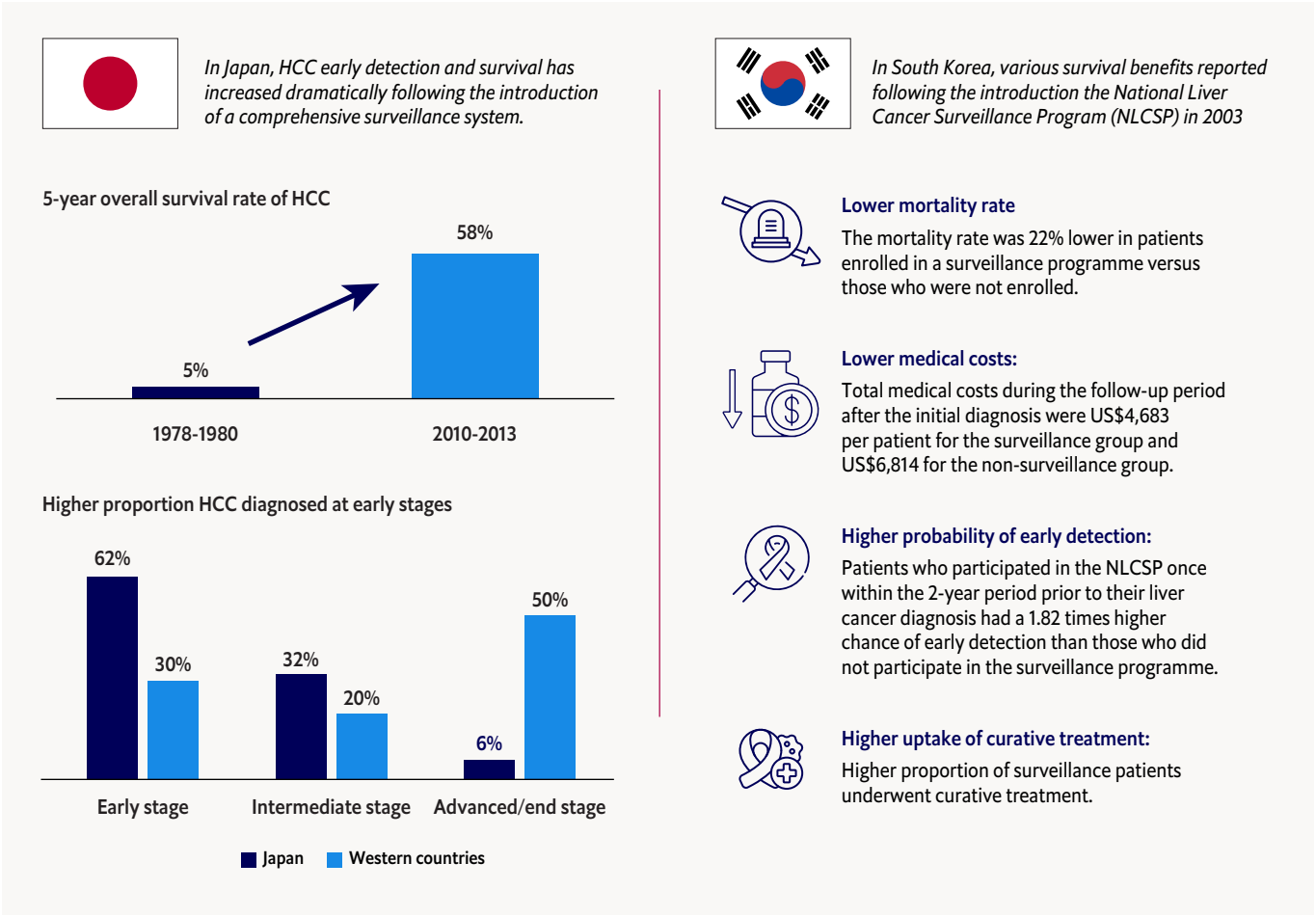
In addition to viral hepatitis or metabolic-associated cirrhotic patients, the Asian Pacific Association for the Study of the Liver (APASL) recommends that those with certain genetic conditions (haemochromatosis and alpha 1 antitrypsin deficiency), with primary biliary

Figure 3. BCLC Stage at diagnosis in North America, Europe and selected Asian economies, 2005 – 2012.



Source: Park et al, 2015.[24]

Figure 4. Examples in Japan and South Korea demonstrating the benefits of surveillance programmes[12, 25, 26,27]



cirrhosis, as well as those with autoimmune hepatitis should undergo surveillance.[22] For chronic non-cirrhotic HBV carriers, APASL recommends an approach that also considers age and ethnicity; the association has identified Asian females aged >50 years and Asian males aged >40 years as targets for HCC surveillance.

Impact of surveillance on patient outcomes

Prognosis for HCC varies across Asia, but is generally better in developed economies.[2] This is especially true for those countries with more advanced screening and surveillance programmes. Surveillance allows for earlier HCC detection and therefore better chances of curative therapy. Asian economies with the longest-running HCC surveillance programmes see a greater proportion of HCC patients diagnosed with early disease than their European or North American counterparts (see **Figure 3**). A retrospective analysis of patients diagnosed with HCC at specialist tertiary centres in Thailand found that surveillance was particularly effective for early diagnosis in patients with metabolic syndrome and advanced liver fibrosis.[23] Nearly half of NAFLD patients in this analysis were diagnosed with very early or early HCC (BCLC stage 0-A).

Figure 5. Limitations of ultrasound and AFP in HCC screening[22,29, 30, 31]

Ultrasound

Lower sensitivity, between 40% and 80%. Furthermore, the sensitivity and specificity is operator-dependent.

Decreased accuracy in obese patients.

Difficult to detect small HCC lesions.

AFP

AFP is not specific to HCC, and levels may be elevated in the presence of other benign liver diseases, such as chronic hepatitis and cirrhosis without HCC. Therefore, it is not recommended for routine surveillance or confirmation of early or small HCC.

AFP has high false-negative rate for detecting small and early-stage tumors.

Organised surveillance programmes have demonstrated significant positive impact (see **Figure 4**). In South Korea, for example, the mortality rate was 22% lower in patients enrolled in a surveillance programme versus those who were not enrolled.[25] Furthermore, a higher proportion of surveillance patients underwent curative treatment.[26] Meanwhile in Japan, the 5-year overall survival rate of HCC increased dramatically from 5% in 1978–1980 to 58% in 2010–2013 following the introduction of a comprehensive surveillance system.[12]

Surveillance modalities

Various testing modalities are available for the surveillance of HCC. These include both imaging techniques and blood-based tumour markers. Ultrasound with or without the tumour marker alpha-fetoprotein (AFP) is the most commonly used screening modality. Both are widely accepted but come with limitations (see **Figure 5**). "The sensitivity and specificity of ultrasound is operator-dependent, and even with specialists, the reliability may be just 50%, especially in cirrhotic patients," says Tawesak Tanwandee, Professor and Chief of the Division of Gastroenterology at Siriraj Hospital, Mahidol University, Bangkok. Furthermore, programmes must determine an appropriate cut-off level for AFP. This is often dependent on whether AFP is used in combination with ultrasound or other imaging, and the degree of viral infection and suppression in the target population.[22] A systematic review found that ultrasound plus AFP is the most cost-effective strategy for HCC surveillance, and it is more cost-effective than ultrasound alone in the majority of settings.[28]

More advanced imaging techniques are used for HCC surveillance in specific scenarios. These include imaging with contrast

"The sensitivity and specificity of ultrasound is operator-dependent, and even with specialists, the reliability may be just 50%, especially in cirrhotic patients"

Tawesak Tanwandee, Professor and Chief of the Division of Gastroenterology at Siriraj Hospital, Mahidol University, Bangkok

ultrasound, magnetic resonance imaging (MRI) and computer-assisted tomography (CT).[22] Dynamic or contrast-enhanced MRI and CT are useful for confirmatory diagnosis or monitoring HCC patients. Several clinical practice guidelines recommend the use of advanced imaging in extremely high-risk patients, or where ultrasound is impractical due to obesity or other medical conditions.[6,32] However, there is insufficient evidence to support their use in routine surveillance,[22] and their cost-effectiveness in population-level programmes remains controversial.[28]

Newer tumour markers, used in conjunction with AFP and ultrasound, offer better sensitivity and specificity, leading to an improved diagnostic performance, in comparison to AFP alone.[20,21] The most established of these newer biomarkers are prothrombin induced by vitamin K absence-II (PIVKA-II), also known as Des-gamma-carboxyprothrombin (DCP), and *Lens culinaris* agglutinin-reactive fraction of AFP (AFP-L3). While these are most-commonly used in diagnostic situations, they have also been adopted in surveillance programmes (see **Box 1** on Japan's surveillance success). AFP-L3 is useful because it can differentiate between increases in AFP caused by HCC from that of other liver diseases.[33] PIVKA-II offers better sensitivity and specificity for HCC, particularly for smaller tumours.[34] Crucially, PIVKA-II can be used as a predictor for prognosis.[35,36].

More recently, the combination of biomarker panels with patient characteristics such as age and gender have enabled the development of statistical diagnostic models and algorithms. These include validated models such as GALAD and GAAD, which combine age and gender with AFP and PIVKA-II/DCP with or without AFP-L3.[37] These models offer the opportunity for improved sensitivity and the potential for diagnosis without the need for ultrasound. However, most of these models have not yet been adopted or validated in real-world settings or in population-level surveillance programmes.[37,38,39]

Programmatic choices about surveillance modalities must consider the local situation and cost-effectiveness analyses. Available data on HCC surveillance in Asia show that surveillance, using various modalities, is considered cost-effective.[28] Critically, cost-effectiveness varies between patient subgroups. Analyses must take into account HCC incidence, the precision of tests used, uptake of surveillance and the incidence of obesity where ultrasound screening may be less effective.[28]

"What we need right now is to have an [evolved] easy and simple list of criteria to define which citizens should receive HCC surveillance"

Masayuki Kurosaki, Director of the Department of Gastroenterology and Hepatology at Musashino Red Cross Hospital, Tokyo

Box 1. Japan: a world-leading HCC surveillance programme

Japan has long been a world leader in the diagnosis and management of liver diseases and viral hepatitis. In fact, many global advances in the diagnosis and management of HCC originate in Japan, and its HCC surveillance programme was first launched as early as the 1980s.[27]

Viral hepatitis is the biggest driver of HCC in Japan, and HCV, in particular, causes a significantly high number of cases. Japan enacted its 2009 Basic Act on Hepatitis Measures to establish free universal testing for HBV and HCV at public health clinics.[40,41] Special subsidy programmes cover anti-viral treatment for HBV and HCV patients.[27] A confirmed viral hepatitis diagnosis is a trigger for referred care and surveillance. In tertiary hospitals, the electronic medical record system is even programmed to prompt a specialist referral whenever a patient receives a positive viral hepatitis test.[12] The surveillance system is also accessible to community hospitals, general practitioners (GPs) and small clinics throughout Japan. Centres that lack appropriate diagnostic capabilities have systems in place to refer patients to larger centres for ongoing surveillance.

Japan's surveillance includes several advanced screening modalities that have been in place for many decades. PIVKA-II was approved and reimbursed in 1989, and AFP-L3 in 1994.[27] Simultaneous measurement of AFP, AFP-L3 and PIVKA-II is encouraged in the surveillance programme funding. The cost for simultaneous testing is ¥2,900 (US$21), as compared to individual AFP, AFP-L3 and PIVKA-II costs of ¥1,010 (US$7), ¥1,900 (US$14) and ¥1,350 (US$10), respectively.[42] Advanced imaging with dynamic CT or MRI or contrast-enhanced MRI is also covered, either in combination with ultrasound for extremely high-risk patients or for those cases that are otherwise difficult to scan using ultrasound.[42]

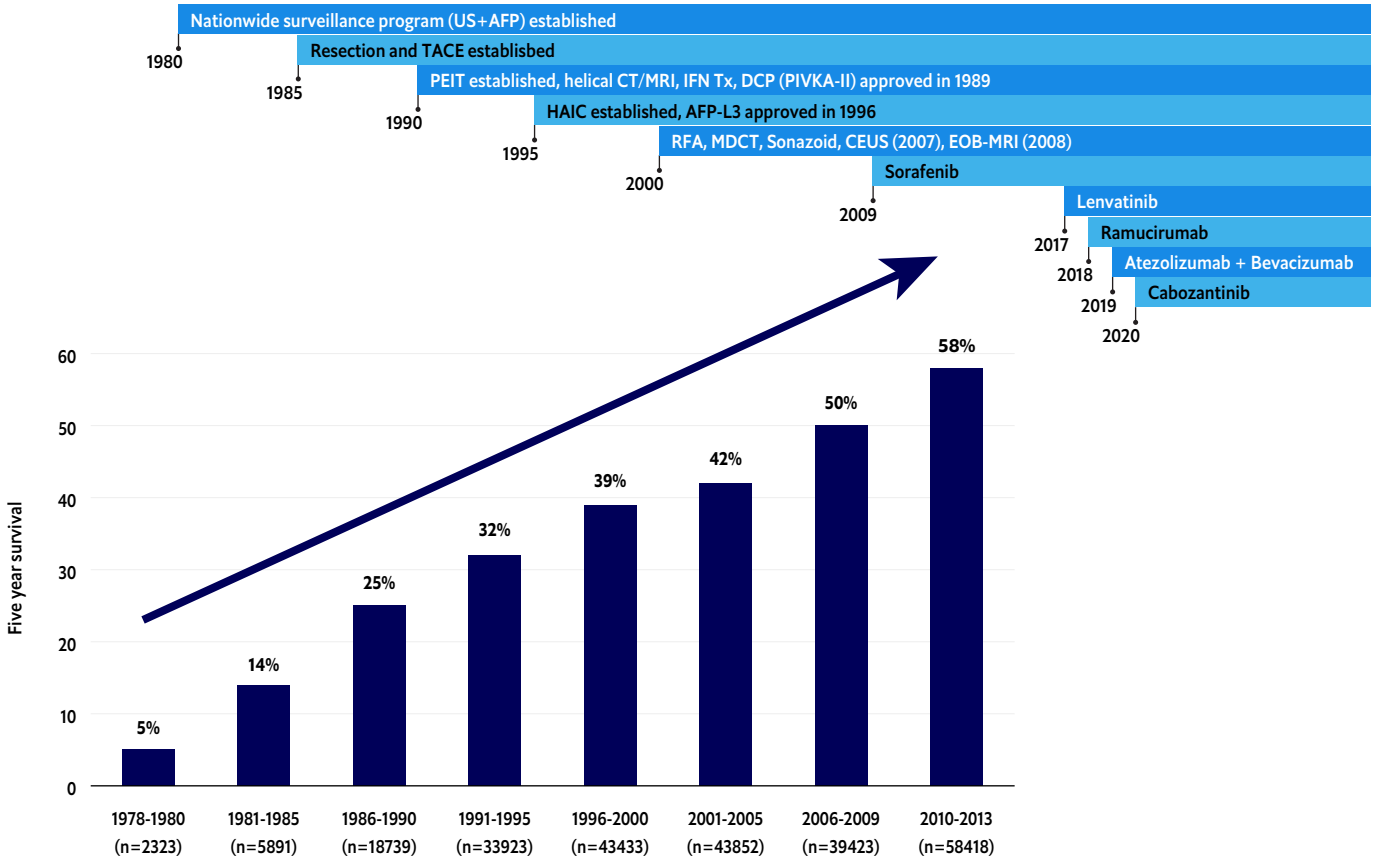
Japan's guidelines delineate those at risk into two groups: high-risk patients (with cirrhosis, chronic HBV or chronic HCV) and, extremely high-risk patients (with cirrhosis caused by active HBV or HCV infections).[42] Surveillance with ultrasound and tumour markers every six months is recommended for high-risk patients. Ultrasound with tumour makers every 3-4 months along with optional dynamic CT/MRI every 6-12 months is recommended for extremely high-risk patients.[32]

Japan's advanced programme is particularly successful in identifying early-stage, treatable HCC with better chances of curative therapy. Only 6% of Japan's HCC cases are diagnosed with advanced disease (stage C-D in the Barcelona Clinic Liver Cancer staging system), which is quite low when compared with the ~50% of cases in Western countries.[27] The impact of early diagnosis, coupled with advances in the management of HCC has allowed Japan to steadily increase patient survival over the last decades (see **Figure 6**). Experts in Japan attribute this to the coordinated efforts by multiple stakeholders, including the national government, academic societies and different local government agencies. [12]

The Japan Society of Hepatology designates a person to be responsible for leading education initiatives in each of Japan's 47 prefectures.[12] The society first launched its "Stop HCC" campaign, targeting both GPs and the general public in 1995.[27] The programme aims to reach non-hepatology healthcare professionals once a year, providing them with information on early detection, diagnosis and treatment of HCC. A separate programme runs public awareness campaigns annually, focused on the importance of early detection. Such campaigns have promoted proactive surveillance efforts.[12]

Successful viral hepatitis control, coupled with changing lifestyles and an ageing population, is changing the characteristics of HCC patients and those at risk. It is increasingly difficult to define which patients with non-viral aetiology are at high risk of HCC and require further screening and intervention. Cases of NAFLD, which includes non-alcoholic steatohepatitis (NASH), are on the rise, and could be missed by the existing surveillance system built around viral causes.[12] "What we need right now is to have an [evolved] easy and simple list of criteria to define which citizens should receive HCC surveillance", says Masayuki Kurosaki, Director of the Department of Gastroenterology and Hepatology at Musashino Red Cross Hospital, Tokyo, "especially among those who don't have a viral infection."

Figure 6. Key milestones in Japan's evolving HCC management strategy and change in 5-year survival rate among patients with all BCLC stage HCC



Source: Adapted from Kudo M, 2023.[12]

(Note: Headers at the top of the figure refer to the different medical and surgical treatment coverage introduced over the years)

Chapter 3. Addressing hepatocellular carcinoma surveillance: current approaches and common challenges

Given the high burden of HCC in the region, Asian economies have made several efforts, with varying degrees of success, to address their needs. The current HCC surveillance initiatives differ in key areas such as national policy support, strategic priority, funding mechanism, awareness initiatives, and implementation across the region. These differences speak to the varying stages of development of such surveillance programmes across Asia. Many Asian economies are yet to implement any coordinated population-based surveillance programme, while some have long-established and well-functioning ones in place. Surveillance efforts are underpinned by evidence-based clinical practice guidelines that adopt a risk-based approach to surveillance. However, recommendations found in such guidelines are not always aligned with surveillance practice. Several other common challenges remain, which are described in this section.

Different coverage levels of national surveillance programmes

The most comprehensive programmes in Asia have nationally coordinated approaches underpinned by legislation and funding commitments for multiple screening modalities. Among these, Japan's national surveillance programme is the most comprehensive and coordinated in the region, and indeed the world (see **Box 1 for more details**). Japan's HCC surveillance programme was launched in the 1980s, in response to the high incidence of HCV-related HCC. It theoretically covers more than 80% of eligible high-risk patients.[12] The programme's coordinated approach includes not only national government agencies, but also academic societies and health practitioners. It is strongly supported by a cancer registry and extensive awareness and education efforts. The programme is notable for its early adoption and funding of more advanced tumour markers—namely PIVKA-II and AFP-L3—and for including advanced imaging.

Second only to Japan in its coverage of and commitment to HCC surveillance, South Korea established its National Liver Cancer Screening Programme (NLCSP) in 2003. The programme is underpinned by legislation, namely the Korean 2003 Cancer Control Act. This act authorises the Ministry for Health and Welfare to organise and conduct systematic surveillance in partnership with public institutions, with management and monitoring performed by the National Cancer Center.[43] The NLCSP identifies targets for screening from the universal National Health Insurance System claims database, and invitation letters are automatically sent to the targeted population once a year.[43] Public health centres are responsible for follow-up, encouraging screening uptake and providing HCC education.[26] Enrolees can attend any clinic or hospital certified as a screening unit. Despite these laudable efforts, Korea's surveillance system remains underutilised (see section below on **lack of awareness and low surveillance uptake**). Furthermore, liver cancer specialists have highlighted that the system targets only existing users of medical services and also does not account for screening in private clinics.[44]

Besides the comprehensive programmes highlighted above, some national plans may target too few at-risk groups, and may not be fully tailored to the local epidemiology. These plans may also have partial elements of recommended surveillance approaches with

some reimbursement gaps. For example, Taiwan introduced its medical care improvement plan for viral hepatitis patients in 2000.[45] This aimed to implement regular HCC screening for high-risk patients. Given the evolving epidemiology in the region, at-risk groups could include patients besides those with viral hepatitis. Additionally, Taiwan's programme recently included funding for PIVKA-II as part of surveillance, but the use of PIVKA-II is not explicitly mentioned in the latest clinical practice guidelines (see **Box 2**).

Lastly, there are certain economies in Asia that have very minimal HCC surveillance initiatives. In Thailand and Vietnam, for example, national efforts are focussed around the control of viral hepatitis, addressing primary HCC prevention rather than surveillance.[46, 47]

Clinical practice guidelines and risk-based approaches

The majority of Asian clinical practice guidelines identify high-risk patients as those with chronic HBV/HCV infection or those with liver cirrhosis.[48] These patients are usually recommended surveillance at 6-month intervals. However, different guidelines adopt different risk categories based on the local epidemiology and clinical practice. Japan is notable for delineating "high-risk" (HBV/HCV infection or cirrhosis of other causes) and "extremely high-risk" (HBV/HCV-related cirrhosis) groups.[32] The recommended interval between surveillance is six months for "high-risk" and 3-4 months for "extremely high-risk" patients (see **Box 1**). Some guidelines, for example those in South Korea, mainland China and Thailand, also consider age and sex in defining high-risk groups.[49] Some guidelines use a risk-based approach to allow for the targeted use of advanced imaging, such as contrast-enhanced ultrasonography and dynamic contrast-enhanced CT or MRI.[48] Despite the wide availability of clinical practice guidelines, implementing their risk-based approaches is not always straight-forward. There are several discrepancies between guidelines and real-world practice (see **Box 2**). These are most often related to the intervals between testing and the availability or funding for different testing modalities.[42, 50-52]

Several risk-scores exist to aid surveillance in Asian patient populations.[53] These mainly focus on HCV-eradicated patients and HBV-suppressed patients, where there is clinical need and a high risk of progressing to HCC. These scores are valuable and could have a more substantial impact if used systematically. Our experts highlight the potential for using risk-scores to triage patients suitable for shorter or longer surveillance intervals. Qing Xie, Director of the Department of Infectious Disease at the Shanghai Jiaotong University School of Medicine, sees the potential for these risk-scores to contribute to the personalised care of HCC patients. "When used correctly, these risk-scores could lessen some of the economic burden around testing and save public health costs," says Dr Xie. At present, however, risk-scores are not routinely used in clinical settings in Asia. "There are so many scoring systems that the big problem is we cannot decide which one is best to use," says Dr Kurosaki. In addition, risk-scores are often manual tools and take away from the already limited patient-physician consultation time. "If there was an automated score that was generated for every patient, that would make it easy", says Jacob George, Professor of Hepatic Medicine and Head of the Department of Gastroenterology and Hepatology at the University of Sydney, "but relying on a clinician to do it [manually] is problematic".

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Jacob George, Professor of Hepatic Medicine and Head of the Department of Gastroenterology and Hepatology at the University of Sydney

Box 2. Taiwan: surveillance success at a crossroad?

Taiwan is a regional leader in viral hepatitis research. Its advanced health system has provided excellent access to vaccination and therapeutics, thereby leading to good patient outcomes. However, Taiwan's progress risks being stalled. "For historic reasons [ie, the high rates of viral hepatitis], liver disease has always been a high priority area [for health policy]," explains Jasmine Pwu, Chief Executive Officer of the Data Science Center at Taiwan's Fu-Jen Catholic University. "Unfortunately, in recent years, new technologies or new added services have been seen as potentially jeopardising the sustainability of the National Health Insurance funding."

A series of population-wide programmes have been introduced to prevent HCC in Taiwan. Taiwan adopted the world's first universal HBV vaccination programme in 1984, and introduced HCC screening with ultrasound as part of its universal health care coverage in 1995.[54] Since then, viral hepatitis surveillance programmes have provided access to antiviral agents, and the National Health Insurance Administration further launched a medical care improvement plan for chronic HBV and HCV patients in 2000.[45] This plan aimed to motivate clinicians to perform an ultrasound every six months for high-risk patients in line with the contemporaneous clinical practice guidelines. Since 2020, PIVKA-II testing has been added as part of the National Health Insurance-funded programme.[45]

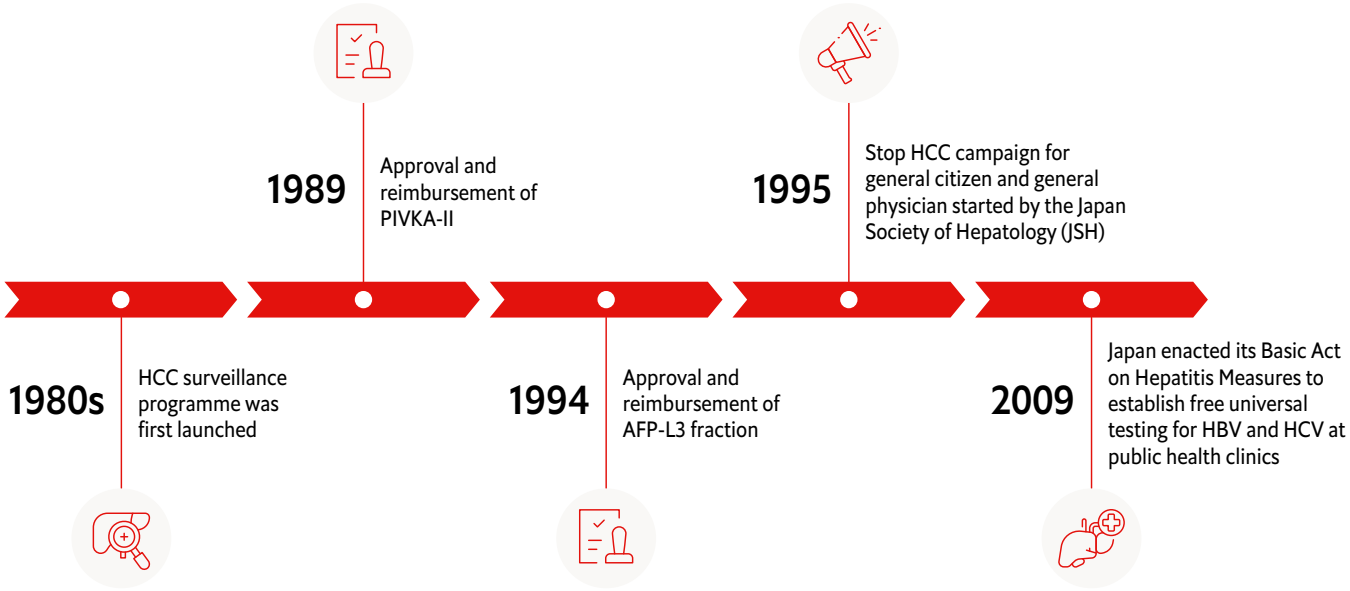
In 2023, major discrepancies continue to exist between the guidelines and real-world practice. For example, the Taiwan Liver Cancer Association's clinical practice guidelines recommends screening with ultrasound and AFP at least every six months, with the option for shorter intervals in high-risk patients.[55, 56] In real-world clinical practice, however, high-risk patients undergo surveillance with ultrasound and PIVKA-II every three months.[45] The downside of the more frequent testing is that the National Health Insurance system will only reimburse PIVKA-II testing twice a year.[45] Another important driver of such discrepancies is poor patient adherence to surveillance. To overcome some of these shortcomings, Ms Pwu shares that Taiwan's administration is now looking at expanding the functionality of the patient-facing National Health Insurance app, which currently only allows access to medical records, but could be used to send screening reminders.

Common challenges to achieving comprehensive surveillance

Political will and national-level strategies

Political will and a national-level strategy are needed to drive comprehensive surveillance of HCC (see **Figure 7** below of the key milestones for Japan's HCC management). This is lacking in many settings, as reflected by the absence of HCC surveillance and management in several national programmes in the region. National liver disease programmes exist in some advanced economies in the region but are not universal. Notably, HCC surveillance is absent from most national cancer control plans despite the evidence of its effectiveness in high-burden settings. Cancer control plans in Malaysia, Thailand, Taiwan, Japan and Hong Kong include HBV vaccination as part of primary cancer prevention.[57-61] Only Hong Kong's 2019 cancer strategy specifically mentions HCC surveillance for high-risk groups, but does not describe any coordinated health system-wide programme.[60]

Figure 7. Summary of Japan's evolving HCC management strategy[27, 41]



The absence of national strategies leads to policy, operational, implementation, financing and reimbursement challenges. These in turn result in missed opportunities for identifying HCC patients and early intervention. The lack of comprehensive HCC prevention strategies in national policies and health benefit packages has been specifically called out as a barrier to implementing surveillance programmes in Thailand.[62] Experts interviewed for this report highlight the benefit of national champions—either within health ministries or influential clinical experts—to drive surveillance uptake.

Financial barriers and sustainable funding

Successful national surveillance programmes must be accompanied by sustainable funding commitments which consider costs, resourcing and long-term sustainability. Good examples of such funding commitments are seen in Japan, South Korea and Taiwan. Japan in particular has employed subsidies across the care spectrum to support access to screening and treatment targeted at HCV patients, the largest at-risk group based on local epidemiology.[63] In South Korea, funding comes predominately from the National Health Insurance budget (80%) with the remaining split evenly between the central government and local governments.[43] However, as budgets are prepared separately, there is the risk of "blind spots" in coverage, which could affect people of lower socioeconomic status.[64]

Where surveillance costs have not been budgeted, additional financial pressure on the health system is observed. For example, in 2014, Thailand conducted a cost-effectiveness analysis of surveillance with ultrasound, AFP, CT and MRI, among other available methodologies, for chronic HBV patients.[62] From the payer perspective, this analysis found that ultrasound, either alone or in combination with AFP, every six months was cost-effective in the Thailand setting.[62] Recently, says Dr Tanwandee, the Thai government has expanded the number of physicians who can diagnose and treat chronic viral hepatitis, which is the main cause of HCC in Thailand. This was however not accompanied by additional budget, meaning that surveillance costs need to be covered by existing hospital overheads. Examples like this suggest the potential need for national programmes to have accompanying national budgets, rather than passing the accountability to regional, provincial or hospital level.

Downstream issues related to reimbursement and OOP payments remain barriers to testing, where it is not fully covered by universal healthcare. Numerous surveys in Asian settings have found that the costs of screening are a barrier for patients, particularly for those of lower socioeconomic status.[30, 65] Considerations of transport costs and lost wages to attend screening are ongoing concerns for such patients. These concerns are especially acute for those patients who are considered "at-risk" and eligible for surveillance, but do not receive timely medical intervention because they do not recognise the benefits of attending screening programmes.

Finally, investment in surveillance programmes is futile unless there is a defined referral pathway with sufficient capacity and funding for effective HCC treatment. There is an important need to improve access to curative care and reduce variation within and across health systems. This is a problem across the region, even where populations are covered by a central payor. For example, an analysis from Thailand's National Health Security Office reimbursement data showed a large disparity in admissions and outcomes for different HCC treatment modalities.[66] Treatment outcomes were best in Bangkok and the South, with median survival more than double than that in the West and East.[66]

Use of data for evidence-based programme design and monitoring

The limited collection and integration of data is an ongoing barrier to building structured and comprehensive surveillance programmes.

Many settings lack detailed data on HCC prevalence and its impact on mortality and quality of life. Investment in such epidemiological data collection is needed to both make the case for surveillance and inform programme design. An example of the importance of such investments is seen in Vietnam where the lack of local data is acute. "More evidence-based data are needed to demonstrate the utility of large-scale surveillance programs for liver cancer early detection," says Doan Dao, Assistant Professor and Director of the Center of Excellence for Liver Disease in Vietnam at Johns Hopkins University, Maryland. Without such information, advocates have limited ammunition to persuade policymakers to implement surveillance, while policymakers lack evidence to make informed decisions.

"More evidence-based data are needed to demonstrate the utility of large-scale surveillance programs for liver cancer early detection"

Doan Dao, Assistant Professor and Director of the Center of Excellence for Liver Disease in Vietnam at Johns Hopkins University, Maryland

Appropriate data sharing and integration is also needed to avoid information silos. Collected data should be used to inform decisions on public health, strategic national cancer or liver disease priorities, health system resourcing and workforce planning. For countries that are yet to implement nationwide surveillance, data is also needed to calculate the cost-effectiveness of surveillance modalities.

Better collection and use of data will also enable professional societies to develop or update clinical practice guidelines to facilitate better consensus, and make recommendations that consider the reality of HCC presentation in individual jurisdictions.

Finally, the effective collection and use of data is vital to track progress and monitor the effectiveness of surveillance programmes. Even in more advanced health systems, data is underutilised. "There is a lot of data available in Taiwan," says Ms Pwu. "It could be better analysed and used to understand the needs and impact of screening programmes." This in turn would allow programmes to be continually optimised to meet evolving needs.

"All radiologists [in Hong Kong] are capable of conducting ultrasound, but there are retention problems keeping skilled practitioners within the public health system. The actual number of qualified radiologists is really limited."

Man Fung Yuen, Deputy Department Chairperson and Chief of the Division of Gastroenterology and Hepatology at the University of Hong Kong

Health system access, resourcing and skill shortages

Effective surveillance programmes must guarantee access for target populations. Access issues can range from a lack of imaging equipment or laboratory capacity to a lack of a trained workforce. In this aspect, there are challenges across the region, particularly in more rural areas. In many developing systems, the volume of patients far outstrips the number of providers. "The problem for Thailand is if you use both ultrasound and AFP, you are working with two specialties—one for the blood test and a radiologist to conduct the ultrasound," says Dr Tanwandee. "In [rural areas], and especially in provincial hospitals, there may be only one or two radiologists, so biannual screenings per patient add up to high workloads, long wait-times and lower uptake for surveillance." A nationwide survey of Thai physicians found that almost half of respondents reported limited access to ultrasound, especially in community hospitals.[70]

Even in more developed systems, wait-times can be long despite the wide availability of low-cost equipment. Man Fung Yuen, Deputy Department Chairperson and Chief of the Division of Gastroenterology and Hepatology at the University of Hong Kong, says it is a resource rather than a skill shortage. "All radiologists [in Hong Kong] are capable of conducting ultrasound, but there are retention problems keeping skilled practitioners within the public health system. The actual number of qualified radiologists is really limited."

Lack of awareness and low surveillance uptake

Lack of awareness of HCC and its risk factors are major barriers to surveillance and significantly impact uptake. Numerous studies in the region link lower knowledge with non-adherence to surveillance. Education and awareness are frequently bigger barriers to screening than cost or access.[67] Lifetime uptake of screening in Korea's national programme is just over 50% of invited target individuals. Lower uptake is seen among older people, men, those with more comorbidities, those living in rural areas, and those with lower socioeconomic status.[26]

Experts interviewed for this paper highlight disparities in knowledge between urban and rural areas, as well as pockets of misconception and stigma experienced by viral hepatitis patients, as important causes of lower screening uptake. Data from China show that "lack of physician recommendation" is a key reason for not accessing HCC screening.[65] This highlights the key role of healthcare workers in delivering education and awareness programmes. Our interviewees highlight that liver disease awareness among doctors is still not optimal. In a survey of Thai physicians, more than half failed to suggest suitable surveillance to patients at risk for HCC, despite widespread belief that surveillance is cost-effective and does not increase physician workload.[68] Lack of awareness is a particular concern in rural and primary care settings, where practitioners have multiple competing priorities and limited consultation time with patients.

Chapter 4. Building 21st Century hepatocellular carcinoma surveillance programmes

Learning from existing surveillance efforts, this research identifies several opportunities to build better and more modern surveillance programmes for Asian economies. These include not only adopting optimal technologies, but also the efficient use of existing resources. The considerations described below are particularly relevant for economies that do not yet have coordinated national programmes.

Adopting optimal technologies to accelerate surveillance

Modern surveillance programmes should make use of more advanced tumour markers that overcome some of the limitations of AFP and ultrasound testing. Despite their long-standing availability, the inclusion of PIVKA-II and AFP-L3 is not optimised in many Asian surveillance programmes. The experts interviewed see particular potential for point-of-care testing and combination tumour marker panels. These could be used for both efficient surveillance and to provide clinical guidance for further investigation and management of HCC. Additionally, biomarker-based statistical diagnostic models could be further explored in the future to potentially facilitate a wider surveillance reach.

The better use of IT systems should be prioritised, especially with the goal of improving access and bringing testing closer to patients. This does not necessarily involve huge infrastructure changes or costs. Dr Xie highlights the use of the internet in China to overcome barriers in delivering services in rural communities by connecting them with larger hospitals and the Chinese Center for Disease Control and Prevention. India has a fairly well-established network of centralised laboratories that can process blood tests as well as imaging studies. However, Dr Shiv Sarin, gastroenterologist and hepatologist; Vice Chancellor of the Institute of Liver and Biliary Sciences, New Delhi and Former Chairman of the Board of Governors, Medical Council of India, shares that it would help to have a centralised digital radiology and application of artificial intelligence (AI) to overcome gaps in the availability and expertise of those who can interpret scans. Existing IT systems can also be configured to automate patient recall and promote better adherence to surveillance activities. This is demonstrated in Japan and Korea and is under consideration in Taiwan (see **Box 1** and **Box 2**).

"It would help to have a centralised digital radiology and application of artificial intelligence (AI) to overcome gaps in the availability and expertise of those who can interpret scans."

Shiv Sarin, gastroenterologist and hepatologist; Vice Chancellor of the Institute of Liver and Biliary Sciences, New Delhi and Former Chairman of the Board of Governors, Medical Council of India

Automation and AI offer exciting opportunities to support surveillance and clinical decision-making. However, this requires a greater degree of investment. Machine learning models can be applied to improve the accuracy of HCC diagnosis with biomarkers, ultrasound and radiological imaging.[69] Data from Japan show that the performance of AI models in distinguishing between benign and malignant

liver tumours is superior to human operators.[70] Automating risk-scores should also be explored to overcome some of the practical limitations of their use. "There is no established consensus on the utility of AI-based systems for HCC prediction," says Dr Kurosaki. "Until a consensus on a standard platform is reached, not many physicians will use it." An opportunity exists to pioneer this in Asia, building on much of the development of risk-scores in the region.

Utilising existing resources and tailoring service delivery

There is no one-size-fits-all approach to HCC surveillance. Building successful surveillance programmes must optimally utilise existing resources and reflect the different needs of affected populations. Programmes may include centralised surveillance, testing and treatment in urban settings, with decentralised care in rural and remote areas. Current examples of comprehensive systems typically occur in single-payer health systems, such as in Japan and South Korea. However, steps are being taken to expand access within other healthcare models. Thailand recently relaxed restrictions on which healthcare practitioners can diagnose and manage chronic viral hepatitis and HCC. "Previously, diagnosis and treatment of hepatitis-related diseases was the preserve of gastroenterologists and hepatologists," explains Dr Tanwandee. "But this has now been decentralised so any doctor can diagnose and prescribe medication, in any level of hospital throughout the country." India, meanwhile, has adopted a bottom-up approach, utilising community healthcare workers to assist in triaging at-risk patients to receive further investigation. This is of particular value for non-viral HCC aetiologies, such as NAFLD, which is the biggest driver of HCC in India and part of its national non-communicable disease programme.[71]

Utilising capacity within the private sector is another option to expand the reach and reliability of surveillance programmes. Here, Dr Yuen points to the example of Hong Kong's colorectal cancer screening programme, which harnesses capacity in private clinics to deliver screening programmes where the public system is limited.[72] Dr Sarin sees the need for additional budget by the government as well as more roles for private insurance companies in covering tumour markers and expanding access. Formalising public-private delivery also offers the chance to close gaps in some of the more advanced HCC surveillance programmes. Specialists from Korea have voiced concerns that their national programme does not account for duplication between the public and private healthcare systems.[44]

Multi-stakeholder engagement to drive a coordinated approach

Adopting a multi-stakeholder engagement approach can ensure more effective participation and accountability among those who make decisions, those implementing them and those affected by them.[73] Such an approach must first engage government stakeholders to build political will. National-level government officials are vital to establish and coordinate surveillance programmes, along with underlying legislation and funding mechanisms. Our experts further highlight that local government health bodies have an equally important role in setting priorities and facilitating screening and referral rates for their populations. Their additional role in funding programmes should also not be overlooked.

Secondly, professional medical societies must champion these surveillance programmes. "Medical societies are usually the engine to drive all these activities," says Ms Pwu. "They can acknowledge the importance of this, generate data and draft plans to share with the [payers] or other [administrative bodies]." There is often a need for a national champion to work with government stakeholders and bridge the gap between patients, academia and policy. Asia is particularly well-positioned in this regard with multiple influential and world-leading experts in viral hepatitis and liver cancers.

Finally, collaborating with patient advocacy groups and non-governmental organisations (NGOs) is increasingly important to drive change. These stakeholders can advocate alongside health officials for the implementation of comprehensive HCC surveillance, and crucially represent the "patient voice" in policymaking. They also have roles in providing peer-to-peer education and support. Patient

advocacy groups tend to be organised around individual diseases or therapy areas, so engaging a broad spectrum of viral hepatitis and cancer organisations will be beneficial.

No one individual or group can drive change alone. "Increasing HCC surveillance is not only dependent on doctors," says Dr Xie. "We must [also] include the government, media, patients and private companies. It takes a union, working together."

Driving awareness nationally among both the general population and physicians

In most of the economies in the region, awareness and education around liver diseases and HCC is fragmented. It is often left to professional associations and NGOs, which may lack the capacity and funding, to deliver comprehensive national programmes. Greater coordination at the national level to increase awareness of HCC among the general population and healthcare providers can help drive the adoption and success of surveillance. This should include encouraging screening in primary care and non-hepatology settings, as well as educating primary care providers on HCC surveillance and referral pathways.

Japan's "Stop HCC" campaign and associated education initiatives are a good example. A 2023 update on the status of HCC in Japan, published in the Liver Cancer journal, stated that the Japan Society of Hepatology's education outreach has "increased knowledge and awareness of the importance of surveillance for high-risk patients" and "in turn promoted proactive surveillance efforts".[12] However, these efforts are long-term commitments and do not often show results overnight or even in the medium-term. "For all the awareness you actually generate in countries at the government level, academic level, primary practice… the reward won't be tomorrow," says Dr George. "But you would have such a good return on investment in the long-term."

"Increasing HCC surveillance is not only dependent on doctors. We must [also] include the government, media, patients and private companies. It takes a union, working together."

Qing Xie, Director of Department of Infectious Disease, Shanghai Jiaotong University School of Medicine, Ruijin Hospital, Shanghai

Conclusions and call to action

There is an extraordinary opportunity to implement comprehensive HCC surveillance programmes in Asia. Excellent examples of surveillance programmes are seen across the region in both high- and lower-resource settings. The following priorities are recommended to advance HCC surveillance:

Include HCC surveillance in national programmes and strategic plans.
Where liver disease burden is high, HCC surveillance and control is vital and should be incorporated into national strategic planning. Depending on the local epidemiology and priorities, this might include stand-alone HCC plans, viral hepatitis control plans or broader cancer control plans. National plans backed by legislation and funding commitments deliver more comprehensive services and demonstrate improved outcomes for HCC patients.

Secure sustainable funding commitments.
Successful programmes must consider long-term resourcing and financing. Funding decisions should be aligned with evidence-based clinical guidelines and best practices, wherever possible. Expanding surveillance programmes without considering the additional costs of testing and resourcing places extra pressure on health systems. The appropriate funding for HCC surveillance is influenced by the existing health financing systems and ability to pay. Reducing inequity in access to surveillance is a key consideration. Economies should explore the additional role of private insurance coverage in expanding access to HCC testing.

Collect, analyse and utilise data to inform programme design.
Modern approaches must prioritise the collection and analysis of data to inform programme design, devise appropriate surveillance modalities and calculate cost-effectiveness. Data on HCC epidemiology, patient outcomes, and the human and economic cost of HCC are needed for efficient HCC care. Better data collection and integration will also enable long-term system optimisation and more robust analyses of programmatic impact and outcomes.

Adopt optimal technologies to advance HCC surveillance.
The region must optimise available technologies based on the local epidemiology and geography. Including newer and more advanced tumour markers can overcome the limitations of ultrasound and AFP testing. This must be supported by clear guidelines and funding commitments. Adapting IT systems to support surveillance programmes can improve access to services and patient recall for both rural and urban areas. With more investment, AI systems could better facilitate risk-based surveillance approaches and streamline the interpretation of test results.

Mobilise existing resources for HCC surveillance.
Successful examples of Asian surveillance programmes utilise the right existing resources to meet the needs of affected populations. This includes expanding the types of healthcare professionals can diagnose and manage HCC, and leveraging existing access points to the health system such as primary care and community health workers. Formalising the use of private healthcare capacity should also be explored.

Engage a broad spectrum of stakeholders to further surveillance goals.
A multi-stakeholder engagement approach should be adopted to drive optimal surveillance programmes. Key stakeholders include national and local government, physicians, patients, advocacy groups, payers and industry. National clinical champions may also help to drive engagement and progress.

Raise awareness and provide education on the need for HCC surveillance.
The awareness and knowledge of HCC and surveillance is suboptimal among both healthcare professionals and general populations. This represents a significant and persistent barrier to surveillance uptake and compliance. There are excellent examples of awareness programmes in the region. Learning from these and applying a coordinated approach to HCC surveillance will offer the best chance for success.

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